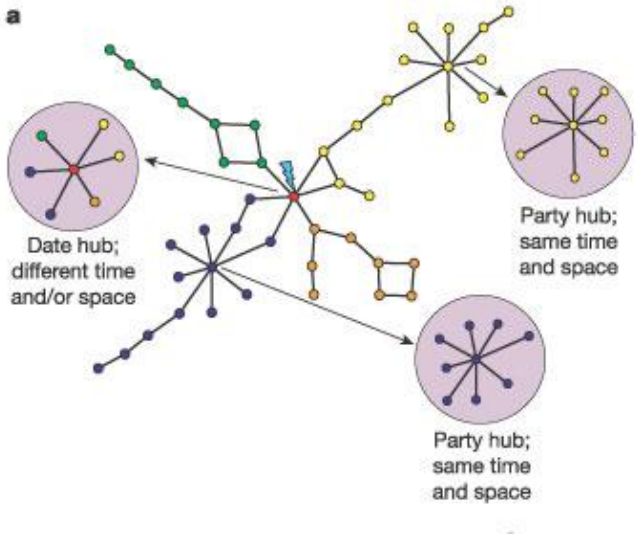
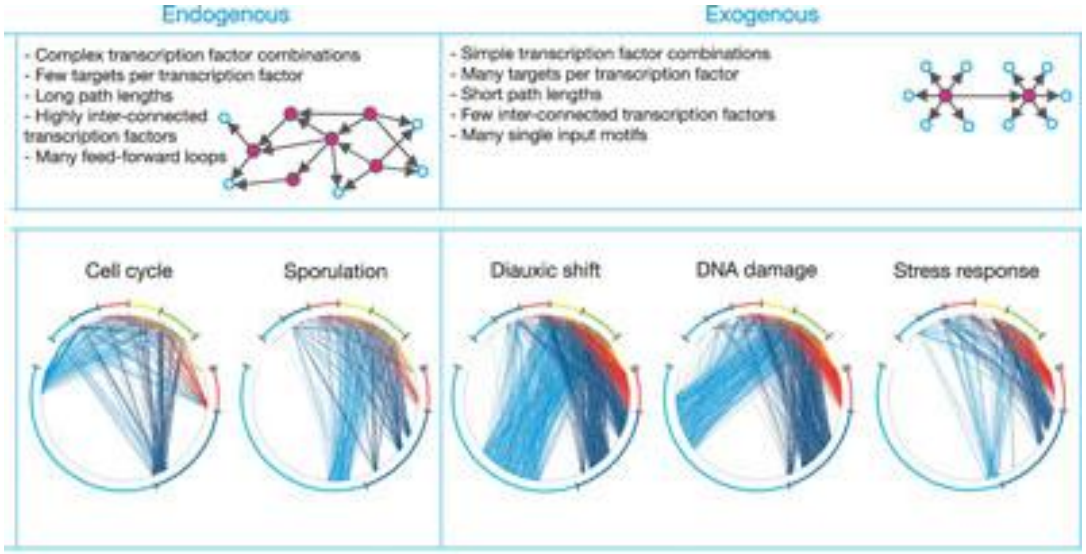
Not all molecular interactions are simultaneously active

Party hubs are inside connected modules that interact simultaneously.
Date hubs connect different modules.



Han et al, Nature 443, 88 (2004)



Condition-dependent transcriptional sub-networks

Luscombe et al,
Nature 431, 308 (2004)

A way of representing dynamics

- Define the network so it encompasses all processes that can happen among the elements included in the network.
- Only a subset of the processes are going on at any given instant. This is because only a subset of the nodes are on (present/active) at any given instant.
- Rather than drawing, deleting and redrawing nodes and edges, we will keep them drawn, but remember that the status of the process represented by the edge depends on the status of the node(s) initiating/regulating the process.
- So, the network is static, and it needs to be supplemented by equations describing the status of the nodes.

Forward and reverse dynamic modeling

Dynamic modeling of interaction network:

Input: components; interactions; states of components

Hypotheses: interaction network; transfer functions; parameters

Output: behavior of components in time

Validation: capture known behavior

Explore: study cases that are not accessible experimentally

change parameters, change assumptions

Reverse problem: Network inference from dynamic information:

Input: components; states of components (in time)

Hypotheses: regulatory framework

Output: proposed regulatory network

Validation: capture known interactions

We will study network inference later in the course.

Types of dynamic models

1. Continuous - similar to chemical kinetics
   - differential equations
2. Discrete - assume a small set of qualitative states
   - the changes in state are given by discrete (logical) rules

1. Deterministic - no randomness is involved in the development of future states of the system
2. Stochastic - non-deterministic in that the next state of is not fully determined by the previous state.
   - can take into account the fluctuations in mRNA/protein numbers and external noise

Continuous and deterministic models: < medium-size networks,
> medium node abundances.
Stochastic models: small networks, low node abundances
Discrete models: > medium networks, multimodal node abundances

Example of continuous model: chemical kinetics

Node status: concentration of the molecule
Assumptions: conservation of mass + elementary reactions
As many equations as many nodes, as many terms as many edges in the bipartite (molecule + reaction) network.

$$A + B \rightarrow C + D$$

Differential equations

$d[A]/dt = -k[A][B]$

$d[B]/dt = -k[A][B]$

$d[C]/dt = k[A][B]$

$d[D]/dt = k[A][B]$

Initial conditions

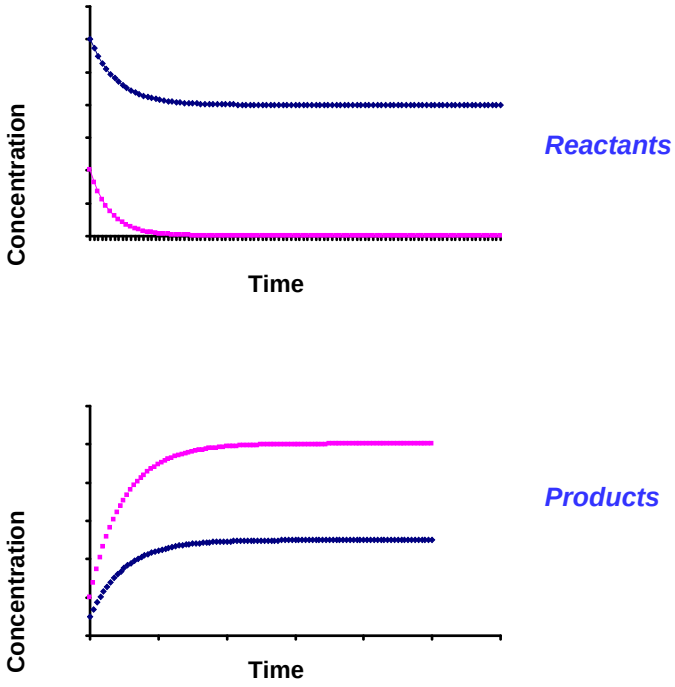
$[A]_{(t=0)} = [A]_0$

$[B]_{(t=0)} = [B]_0$

$[C]_{(t=0)} = [C]_0$

$[D]_{(t=0)} = [D]_0$

Concentration Time Course



Q. When does the reaction stop?

Another, flux- based look at the problem

Reaction Pathway

A + B → C + D (1)
A + D → E (2)
B + C → F (3)

Stoichiometric Matrix (S)

Molecules	Reactions 1	2	3
A	-1	-1	0
B	-1	0	-1
C	1	0	-1
D	1	-1	0
E	0	1	0
F	0	0	1

$$\frac{dx}{dt} = \boldsymbol{S}\boldsymbol{v}$$

Vector of metabolite concentrations

Vector of reaction fluxes

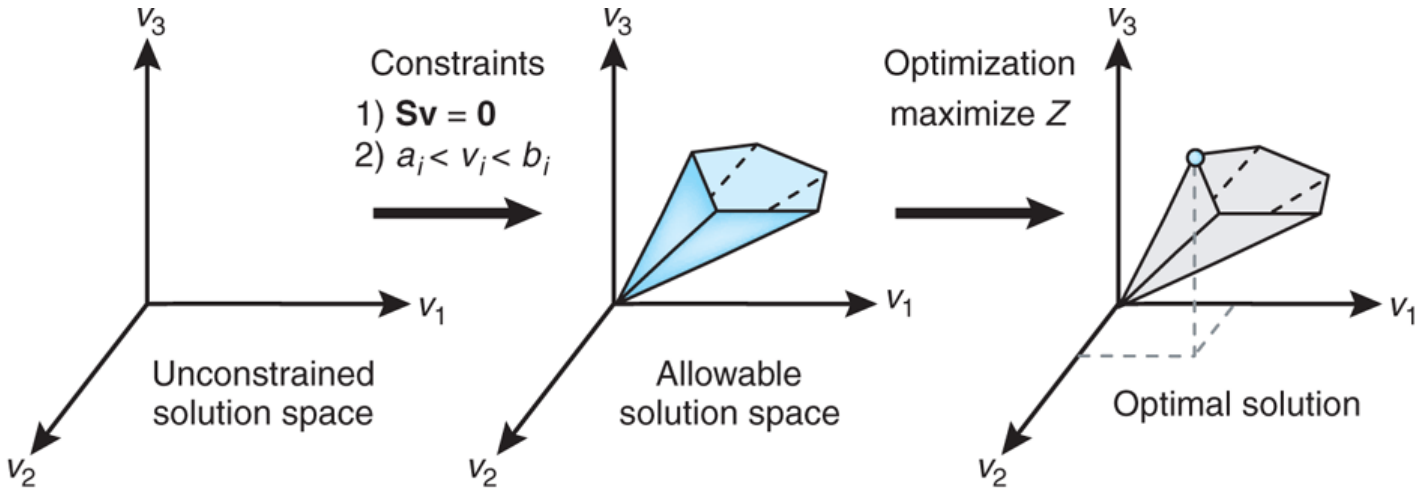
$$\begin{bmatrix} d[A]/dt \\ d[B]/dt \\ d[C]/dt \\ d[D]/dt \\ d[E]/dt \\ d[F]/dt \end{bmatrix} = \begin{bmatrix} -1 & -1 & 0 \\ -1 & 0 & -1 \\ 1 & 0 & -1 \\ 1 & -1 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} \times \begin{bmatrix} v_1 \\ v_2 \\ v_3 \end{bmatrix}$$

In a steady state the fluxes balance each other and the concentrations are constant

$$\boldsymbol{S}\boldsymbol{v} = 0$$

Flux balance analysis

- The number of reactions is much larger than the number of metabolites, so one cannot find a unique steady state.
- Instead, use constraints and optimization principles to find a feasible steady state
- Constraints: bounds on fluxes or concentrations
- Optimization: maximize the production of biomass (growth).



Bernhard Palsson, Systems Biology: Properties of reconstructed networks

Enzyme-catalyzed reactions

Most reactions in biological systems would not take place at perceptible rates in the absence of enzymes.

Enzymes are specialized proteins that bind specific reactants, get them close together, and by this, accelerate the reaction up to a million times.

In this context, the reactants are called substrates.

In enzyme-catalyzed reactions the rate of product synthesis depends nonlinearly on the concentration of the substrate.

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Michaelis-Menten model of enzymatic reactions

Leonor Michaelis, Maud Menten (1913)

1. A specific enzyme-substrate complex is a necessary intermediate in catalysis
2. This complex is in a quasi-steady state
3. The step that yields the product is irreversible

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \overline{ES} \xrightarrow{k_2} E + P$$

Ex. Draw two possible network representations of this process.

Michaelis-Menten kinetics (cont.)

$$\boldsymbol{E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \overline{ES} \xrightarrow{k_2} E + P}$$

Goal: express the rate of product synthesis as a function of substrate concentration

$$\left.\begin{aligned} \left[\overline{ES}\right] &= [ES]\frac{k_1}{k_{-1}+k_2} \\ \left[E_T\right] &= [E] + \left[\overline{ES}\right] \\ \boldsymbol{K_M} &= \boldsymbol{\frac{k_{-1}+k_2}{k_1}} \end{aligned}\right\} \quad \frac{d[P]}{dt} = k_2\left[E_T\right]\frac{[S]}{K_M + [S]}$$

Ex. Draw the dependence of the rate of product synthesis on the substrate concentration. Characterize three limits/points on the curve.

Enzyme-catalyzed reactions

$$\frac{d[P]}{dt} = k_2[E_T]\frac{[S]}{K_M + [S]}$$

K_M is equal to the substrate concentration at which the reaction rate is half its maximal value.

Limit 1 $$[S] >> K_M \Rightarrow \frac{d[S]}{dt} \approx k_2[E_T]$$

k_2E_T is the number of substrate molecules converted in a unit time when the enzyme is fully saturated with substrate.

Limit 2 $$[S] << K_M \Rightarrow \frac{d[P]}{dt} \approx \frac{k_2}{K_M}[E_T][S]$$

The efficiency of an enzyme can be described by k_2 / K_M

Chemical kinetics-like models of cellular processes

Assumption: cellular synthesis and degradation processes can be described as simple or enzyme-catalyzed reactions

Ex.: receptor - ligand binding

methylation reactions – catalyzed by methylating enzymes,

phosphorylation - catalyzed by kinases

dephosphorylation – spontaneous or catalyzed by phosphatases

protein synthesis –catalyzed by mRNA,

protein degradation – spontaneous or catalyzed

J. Tyson, K. Chen, B. Novak, Curr. Opin. Cell Biology 15, 221 (2003)

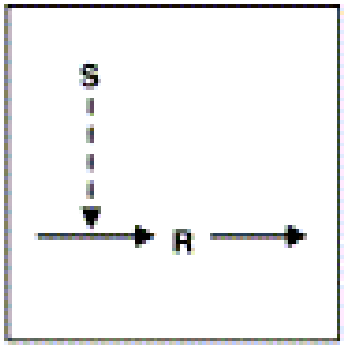
Protein synthesis and degradation

Protein synthesis: mRNA → protein (sufficient supply of amino-acids)

Protein degradation: protein →

Notations in Tyson et al 2003: The source element (here the mRNA) is denoted S (for signal). One component (here the protein) is designated as the response.

Network diagram:



Solid edge: mass flow
Dashed edge: regulation

Q: Draw an alternative network, more in line with what we have seen before, where edges connect two nodes and signify regulation.

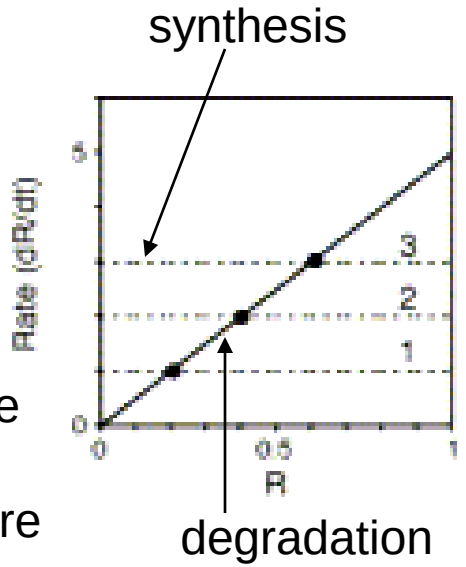
Kinetics of protein synthesis and degradation

Protein synthesis: mRNA → protein (sufficient supply of amino-acids)

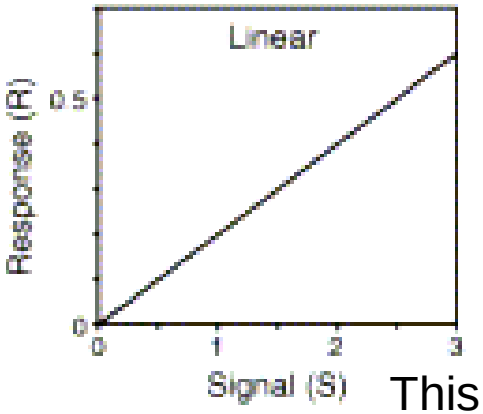
Protein degradation: protein →

$$\frac{dR}{dt} = k_1 S - k_2 R$$

Steady state: $R_{ss} = \frac{k_1 S}{k_2}$



The points where the synthesis and degradation terms are equal indicate the steady states.



This is the input-output characteristic of the system.

Kinetics of phosphotransfer

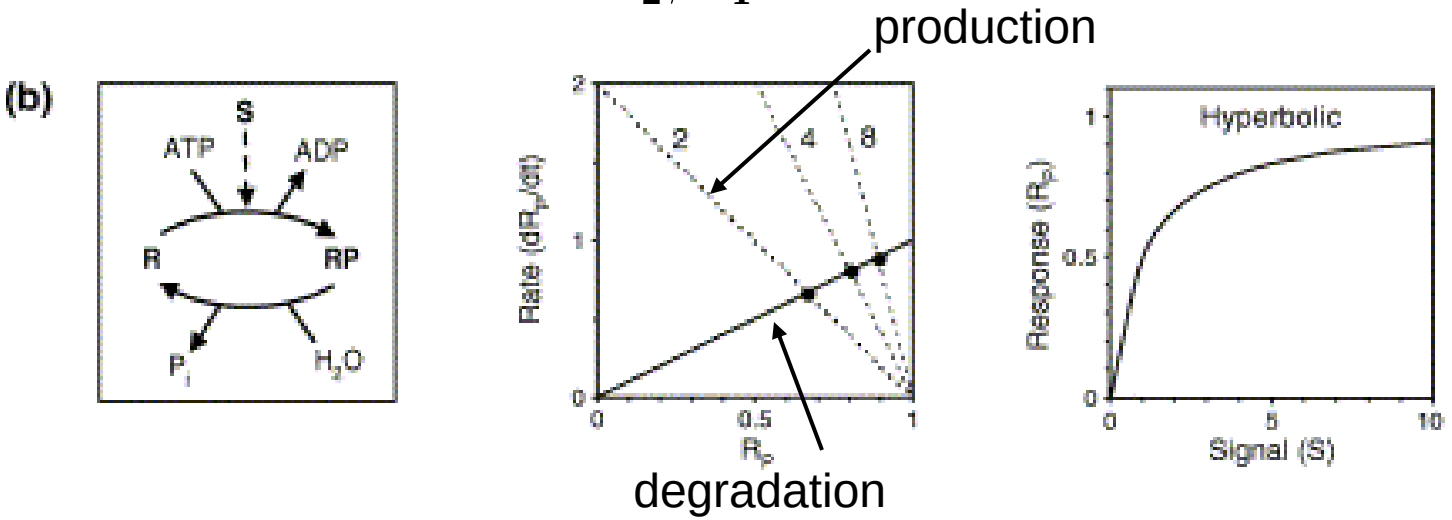
Phosphorylation: protein → phospho-protein

Dephosphorylation: phospho-protein → protein

The first reaction is catalyzed by a kinase, assume first –order kinetics

$$\frac{dR_P}{dt} = k_1 S R - k_2 R_P \qquad R_T = R + R_P$$

Steady state: $$R_{P\,ss} = R_T \frac{S}{k_2 / k_1 + S}$$



Phosphotransfer with Michaelis-Menten kinetics

Assume that the phosphorylation and dephosphorylation reactions follow Michaelis-Menten kinetics

$$k_1 S R \rightarrow k_1 S \frac{R}{K_{M1} + R} \qquad k_2 R_P \rightarrow k_2 \frac{R_P}{K_{M2} + R_P}$$

Steady state: $$R_{P\,ss} = R_T G\left(k_1 S, k_2, \frac{K_{M1}}{R_T}, \frac{K_{M2}}{R_T} \right)$$

G - Goldbeter-Koshland function